REMARKS

Claims 93-169 are in this case and have been allowed. This response if filed to correct formalities in the specification.

Minor clerical errors and spelling error have been corrected in paragraphs on pages 2-4. An erroneously repeated phrase is deleted from the paragraph bridging pages 4 and 5.

On page 20, line 15, the word "cross-coupling" has been replaced with "homocoupling." It is clear from the context of the specification on page 20 that it is homocoupling that is intended to be minimized or eliminated.

Page 21, line 8 has been amended to replace 'Table 6" with "Table 5." It is clear from a comparison of the description at this point in the specification and Table 5 that Table 5 was intended.

On page 31 spelling errors have been corrected on lines 4 and 14. On page 38, line 6 another spelling error has been corrected.

On page 39, line 29, a word is missing from the sentence. The phrase intended was "compromise between reactivity and selectivity." This amendment is made for clarity.

On page 45, spelling and other clerical errors are corrected on lines 10, 13, and 20.

Spelling and clerical errors have been corrected on page 9. In particular, a phrase in the last line of the paragraph "in the freezer indefinitely" which was obscured in the specification as filed is made clear.

On page 98, the last line on the page a partial sentence has been removed. The partial sentence is not necessary for enablement or description and has been removed to imporve clarity.

The specification has been amended at the request of the Examiner to replace several chemical equations and formulas therein. No new matter has been added to the specification. In general the Examiner's concern was the legibility of the chemical formulas.

Matter that is to be deleted is positioned within double brackets "[[ ]]" and material to be added is underlined in the amendment pages herein.

In cases in which Tables have been replaced, the entire Table has been deleted and replaced with a replacement Table. For the convenience of the Office, the undersigned attaches replacement pages 27, 29-31, 42, 43, 133 and 134 to facilitate amendment of the specification. The new pages are consistent with the amendments made herein and do not contain new matter. Chemical structures and/or equations have been replaced with improved drawings of those structures or equations on pages 27, 29, 30, 31, 42 and 43. Tables on pages 133 and 134 have been replaced.

Table 17 on page 133 has been replaced in order to provide a more legible chemical equation, and delete and extraneous "*" in column 4, data row 4 of the table. To facilitate the amendment procedure, original Table 17 which was printed in landscape orientation has been reduced in size and placed in double brackets. New Table 17 has been resized so that it can be printed in portrait orientation. The entire new Table has been underlined. We have used this form for making amendments because it seemed consistent with the new rules and clear. If the procedure employed by the undersigned to indicate amendments of the Tables is formally incorrect, the undersigned requests a telephone conference with the Examiner to discuss how to correctly make amendments of this type under the new rules. It is believed that the submission of replacement pages will facilitate amendment by the Office.
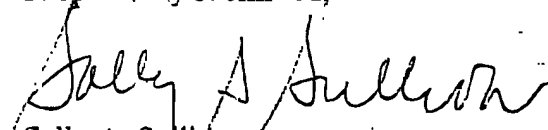
Table 18 on page 134 has likewise been amended to improve legibility of chemical structures. The Table as amended is formatted in portrait orientation.

None of the amendments adds new matter to the specification. The amendments herein are believed to obviate all objections to the specification. The application contains no drawings so all drawing formalities are believed to have been met.

This application being in condition for allowance passage to issuance is respectfully requested.

This amendment is accompanied by a Petition for Extension of Time a check in the amount of $475. If the enclosed fee is incorrect, please charge any deficiency or credit any overpayment to deposit account 07-1969.
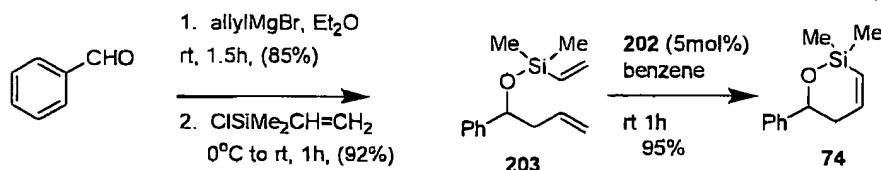
Respectfully submitted,

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lem:November 20, 2003

RCM of the sterically more demanding vinylsilyl ether dienes requires the less sterically sensitive molybdenum carbene complex $(CF_3)_2MeCO]_2Mo(=CHCMe_2Ph)(=NC_6H_3-2,6-i-Pr_2)$ (202), developed by Schrock et al.(33).

To test the feasibility of the overall transformation, combining the two types of reaction the vinylsilyl ether, 203, was prepared as a starting material for RMC by addition of allylmagnesium bromide to benzaldehyde followed by silylation with commercially available chlorodimethylvinyl-silane. Initial studies on the RCM reaction of 203 using the Grubbs alkylidene complex none of the desired ring-closure product 74, was observed. All variations in conditions, including change of solvent and/or temperature were unsuccessful. Substrate 203 did undergo the RCM process when the molybdenum complex 202 was used as the catalyst. After careful optimization a near quantitative yield of 74 was obtained with 5 mol % of 202 in benzene at ambient temperature.
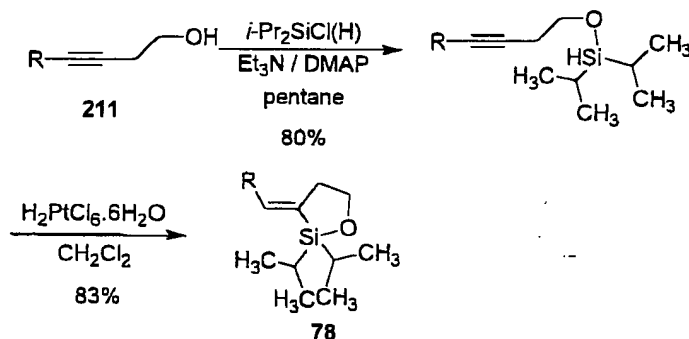

The influence of tether length (i.e., ring size) and substituents on the RCM/cross-coupling process was examined as shown in Table 25. The allylic ether 207a (a five-membered ring precursor) suffered RCM under the standard conditions (5 mol % of Mo complex in benzene, 1 h); however, only 75% conversion could be obtained in 1 h. This problem was solved by increasing the catalyst loading; using 7 mol % of catalyst,the complete consumption of 207a was achieved within 3 h to afford the product 208a in 89% yield (Table 25, entry 1). However, for the preparation of seven-membered siloxane 208d, the reaction only went to 91% completion, giving an 81% yield under these conditions. With a monosubstituted alkene or monosubstituted vinylsilane (entries 2 and 3), the RCM process proceeded slowly compared to 74 albeit ultimately to completion. Unfortunately, substitution on both the alkene and vinylsilane (entry 4) did not lead to successful closure (even under harsher conditions), presumably as a result of the significant increase in steric demand.

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The results illustrated in Table 25 demonstrating successful RCM reaction to form the cyclic siloxanes (such as 74) along with the results of successful cross-coupling reactions of those siloxanes illustrated in Tables 13 and 14 demonstrate the viability of sequential RCM/cross-coupling reactions employing readily available silyl ethers. The cycloalkenylsiloxane serves as a competent donor undergoing rapid and high-yielding cross-coupling with various aryl and alkenyl halides.

Intramolecular Hydrosilylation combined with Cross-Coupling

Facsile cross-coupling reactions of this invention are observed with organosilicon reagents having oxygen function on the silicon, e.g., alcohols, ethers or disiloxanes. Starting materials for the coupling reactions herein can be obtained by intramolecular hydrosilylation of a pendant silyl ether (35). This process provides an unambiguous route to geometrically defined vinyl silanes having an oxygen function. This strategy, as illustrated in Scheme 14, is exemplified for the preparation of stereo defined homoallylic alcohols.
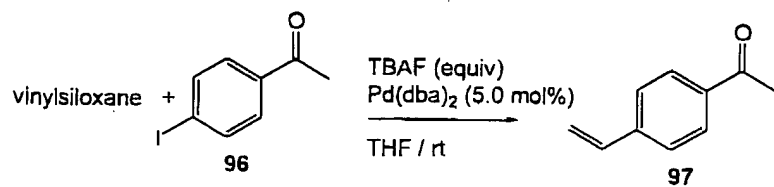
In particular, the cyclic siloxane 78 (where R is CH_3-) derived from 3-pentyn-ol (211, where R is CH_3-) was examined to illustrate the combination of intramolecular hydrosilylation and cross-coupling of this invention. Silylation of the alkynol with diisopropylchlorosilane provided a silyl ether in good yield which was then subjected to intramolecular hydrosilylation using a catalytic amount of Speier's catalyst:

Palladium cross-coupling reaction of 78 with various aryl iodides are examined in Table 15, discussed above. Attempts to extend the intramolecular hydrosilyation to dimethyl siloxanes resulted in the generation of undesired polymeric materials. A practical solution to this problem was the establishment of a one-pot protocol that obviated the isolation and purification of delicate silyl ethers and siloxanes and improved overall efficiency of the process.
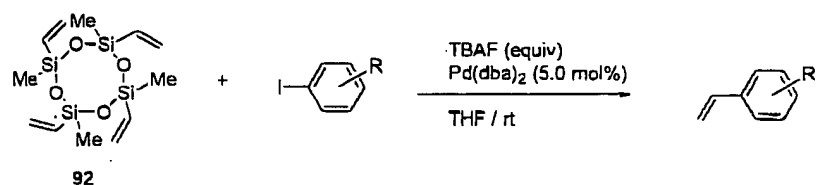
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Table 17

Optimization of the coupling of vinylpolysiloxanes with 96

Entry	Vinylsiloxane (equivalents)	TBAF (equivalents)	Time (min)	Conversion (%)
1	92 (1.2/4)	2.0	10	100 (88)
2	93 (1.2/3)	2.0	10	100 (85)
3	94 (1.2/3)	2.0	10	100(89)
4	95 (1.2/6)	2.0	10	78
5	95 (1.5/6)	2.0	10	94 (51)
6	95 (1.5/6)	2.0	10	93 (53)

*The numbers in parentheses are isolated yields from 2.0 mmol scale experiments.
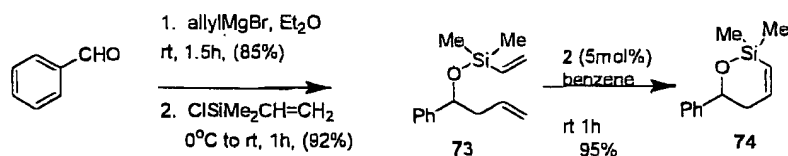
Table 18
Cross-coupling of 92 (DY) with aryl iodides[a]

Entry	Aryl R	92 (equiv.)	TBAF (equiv)	Time (min)	Product	Yield (%)
1	4-COMe (96)	1.2/4	2.0	10	97	88
2	4-COMe (96)	1.2/4	2.0	10	97	80
3	4-COOEt (98)	1.2/4	2.0	10	99	85
4	4-COOEt (98)	1.2/4	2.0	60	99	83
5	4-OMe (100)	1.5/4	3.0	240	101	46
6	4-OMe (100)	1.5/4	3.0	360	101	63
7	3-NO$_2$ (102)	1.2/4	2.0	10	103	87
8	3-CH$_3$OH (104)	1.2/4	2.0	480	105	59
9	2-OMe (106)	1.5/4	3.0	24h	107	72
10	2-COOMe (108)	1.2/4	2.0	480	109	83
11	1-naphthyl-I (110)	1.2/4	2.0	180	111	64

[a] All the reactions were conducted under argon on 2.0 mmol scale.
[b] 4-Iodoacetophenone added last over 45 min at <30°C.
[c] 1 mol% Pd(dba)$_2$ loading.
[d] 10 mol% AsPh$_3$ added.

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Previous experience with handling silanols suggested that increasing the bulk of the silicon substituent could make the products more tractable. Since hexaisopropylcyclotrisiloxane is not commercially available. An alternative procedure that involves (1)lithiation of the vinyl ether, (2) addition to chlorodiisopropylsilane (to form the intermediate silyl hydride), (3) oxidation of the hydridosilane with chlorine to form the chlorosilane, and (4) alkaline hydrolysis to produce the silanol can be employed to prepare silanols useful in the cross-coupling reactions herein.
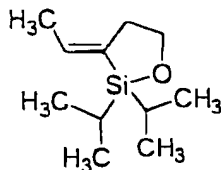
Cyclic silyl siloxanes

The cyclic silyl siloxane **74** was prepared by ring-closing metathesis (RCM) using the molybdenum carbene complex **72** [(CF$_3$)$_2$MeCO]$_2$Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-2,6-i-Pr$_2$) developed by Schrock et al.(33):

Optimization of the Pd(0)-catalyzed coupling with siloxane **74** and 4-iodoacetophenone employed the conditions developed with alkenyl silanols. Thus, siloxane **74** was combined with a 1.0 M THF solution of tetrabutylammonium fluoride (TBAF·3H$_2$O) at room temperature, followed by the addition of 4-iodoacetophenone and 5 mol % of Pd(dba)$_2$, sequentially. The reaction proceeded cleanly to completion in only 10 min. Decreasing the loading of Pd(dba)$_2$ only marginally affected the rate of the coupling process. However, with a lower catalyst loading (1.0 mol %) or less TBAF (1.0 equiv) the reaction did not go to completion and a significant amount of 4-iodoacetophenone was recovered.

With suitable conditions for the cross-coupling processing hand, the reaction was examined with various aryl iodides. Both the nature and position of substituents on the aromatic ring were studied. The results compiled in Table 13 reveal high compatibility with the common functional groups tested. For all aryl iodides examined, the reaction gave uniformly high yields. Noteworthy features of this process include the following: (1) electron-withdrawing or
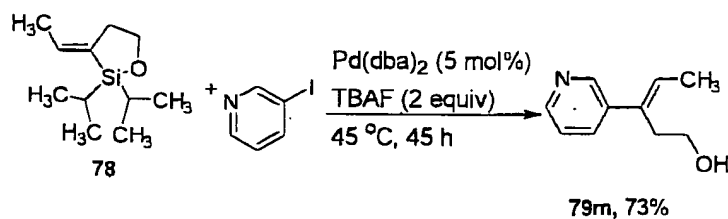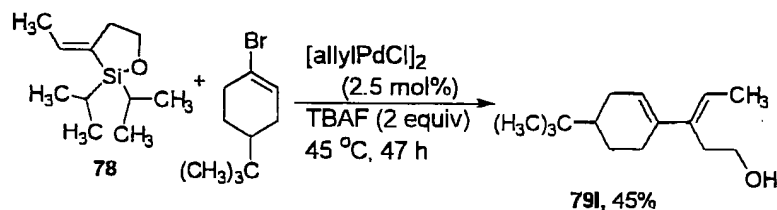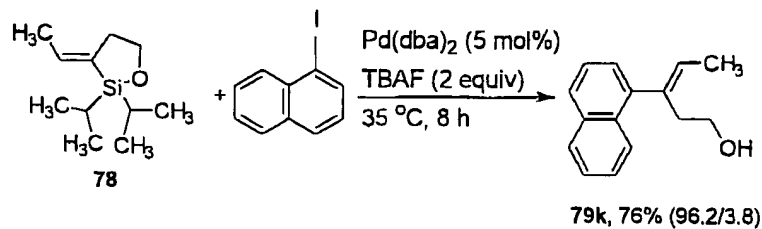
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Siloxane **78** was dissolved in 2.0 equiv of a 1.0 M solution of TBAF in THF, followed by the addition of iodobenzene and 5 mol % of Pd(dba)2. The siloxane did undergo the coupling process, however, at a significantly reduced reaction rate compared to the related silanols. Moreover, the reaction mixture was contaminated with a substantial amount of biphenyl (the product of self-coupling of iodobenzene), and thus the yield of the cross-coupling product was attenuated. The addition of various ligands or decreasing the amount of Pd(0) did not meaningfully improve the results. It was found, however, that adding the iodide in portions satisfactorily suppressed the formation of biphenyl and correspondingly improved the yield of the desired coupling product. The portionwise addition of the iodide proved to be effective in reducing the amount of homocoupling byproduct in most cases. For a few, very slow reacting substrates, even this expedient was not helpful.

With a reproducible procedure in hand, the scope of the reaction with regard to the nature and position of substituents on the aromatic ring was explored The results compiled in Table 15 reveal good compatibility with all common functional groups tested (ester, ketone, nitro, alcohol, nitrile, ether). For all aryl iodides examined, the reaction proved to be mild and high yielding except in the case of 2-nitroiodobenzene (entry 4) which was very slow and gave a substantial amount of nitrobenzene as a byproduct. Noteworthy features of this process are that (1) electron-withdrawing or electron-donating groups exhibit similar reactivity, (2) ortho substituents on the aryl iodide do not affect the reactivity significantly, (3) the reaction tolerates diverse functional groups such as ester, nitro, cyano, ether, and even free hydroxy group, and (4) the reactions of all halides were stereospecific, with the exception of 4-nitroiodobenzene and 1-iodonaphthalene, which gave a small amount of the geometrical isomer.

This variant of the coupling reaction is not limited to benzene derivatives. For instance, 1-iodonaphthalene, 1-bromo-4-tert-butyl-1-cyclohexene (an unactivated vinyl bromide),and 3-iodopyridine reacted with **78** to give the expected products **79k**, **79l**, and **79m**, respectively, in reasonable to good yield:

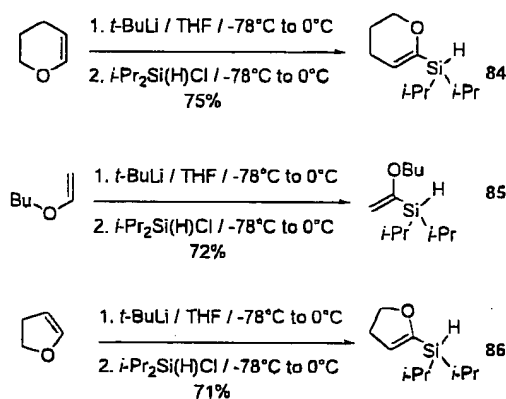**79k, 76% (96.2/3.8)**

79l, 45%

79m, 73%

The optimization of this process next turned to the investigation of the importance of the silicon substituents. It was of interest to see whether and how the size of the substituents on the silicon would affect the rate and selectivity of the reaction. Additional benefits such as improved mass efficiency and ease of by-product removal could be realized with a smaller group in place of an isopropyl group. We thus focused our attention on the corresponding dimethylsiloxane.

However, the synthesis of the siloxanes was problematic. The intramolecular hydrosilylation of dimethylsilylethers with chloroplatinic acid resulted in polymeric materials. Though the platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex (Pt(DVDS)) gave clean in-tramolecular hydrosilylation, any attempts to obtain the siloxane in a pure state or to scale-up the preparation of the siloxane led to oligomerization.

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A practical solution to this problem was conceived in the form of a one-pot protocol that would (1) obviate the need to isolate and purify the delicate silyl ether and siloxane and (2) improve the overall efficiency of the process. Thus, to streamline the procedure and minimize the formation of potentially deleterious byproducts, tetramethyldisilazane (TMDS) was employed as the silylating agent. The one-pot process is discussed below.

Silyl Hydrides

Silyl hydrides are useful precursors for cross-coupling, particularly in those cases where the hydroxyl functionality would not be tolerated. Scheme 7B illustrates the reactions of silyl hydrides with aryliodides. Silyl hydrides were prepared as exemplified for hydrides **84-86**:

Subjecting the hydridosilane **84** and 2-iodotoluene to the reaction protocol optimized with silanols gave rise to only a small amount of coupling product along with 1,5-diphenyl-3-pentanone from reduction of dba. The evolution of a gas when the silane was mixed with TBAF suggested that the silyl hydride was being hydrolyzes. It is well-known that hydrolysis or alcoholysis of silyl hydrides can be catalyzed by fluoride ion at room temperature to liberate hydrogen gas. Thus, it appeared that the coupling product observed could be the result of silanol generated *in situ* from the silyl hydride.

The reaction protocol was slightly modified to examine whether or not in situ generation of the silanol from the silyl hydride could be used to obtain cross-coupling. Thus, the silyl hydride was first combined with TBAF (the activator) for 1-20 min. at room temperature until no further gas evolution was observed at which point the organic iodide and

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